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REVIEW

Cannabidiol as a potential treatment for psychosis

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Abstract
Although cannabis use is associated with an increased risk of developing psychosis, the cannabis constituent cannabidiol (CBD) may have antipsychotic properties. This review concisely describes the role of the endocannabinoid system in the development of psychosis and provides an overview of currently available animal, human experimental, imaging, epidemiological and clinical studies that investigated the antipsychotic properties of CBD. In this targeted literature review we performed a search for English articles using Medline and EMBASE. Studies were selected if they described experiments with psychosis models, psychotic symptoms or psychotic disorders as outcome measure and involved the use of CBD as intervention. Evidence from several research domains suggests that CBD shows potential for antipsychotic treatment.

Contents

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1. Introduction

1.1. Background

Since the introduction of new generation atypical antipsychotics in the 1990s, few clinically meaningful new treatment options for schizophrenia have emerged despite a persistent need. Schizophrenia remains a highly invalidating disorder (van Os and Kapur, 2009) with a lifetime prevalence of 0.3–0.6% (McGrath et al., 2008).

Several lines of etiological research implicate cannabis use as a, probably modest, risk factor for psychotic illness in general and schizophrenia in particular (Myles et al., 2012; Grech et al., 2005; Rapp et al., 2012; Zammit et al., 2002; van Os et al., 2002; Manrique-Garcia et al., 2012). Delta-^{9}-tetrahydrocannabinol (THC) is one of the 70 phytocannabinoids (Mechoulam et al., 2007) that can be found in the *Cannabis sativa* plant and is thought to be the main psychotropic agent of the cannabis (Pertwee et al., 2007). THC is dose dependently associated to psychiatric symptoms such as psychotic like experiences in several studies (Schubart et al., 2010; Moore et al., 2007).

In contrast, in 1974 the cannabis plant constituent cannabidiol (CBD), was reported to interfere with the psychomimetic actions of THC (Karniol et al., 1974) providing a first indication that CBD may have potential as an antipsychotic agent as later suggested by Bhattacharyya et al. (2010).

1.2. Outline

This paper first provides a brief overview of the endocannabinoid system (ECS) and a concise description of the role of the ECS in the neuropathology of psychotic disorders. Then we will review currently available animal, human experimental, imaging, epidemiological and finally clinical studies that investigated the antipsychotic properties of CBD. Reviews are available focusing on the effects of cannabidiol on psychosis (Zuardi et al., 2012), on the relationship with neuroimaging findings (Batalla et al., 2013; Bhattacharyya et al., 2012a, 2012c) and the potential neuroprotective effects of cannabidiol in the context of neuro-imaging studies (Hermann and Schneider, 2012). This review stands out by providing an overview of neuropathological background including the endocannabinoid system and neuro-immune response.

2. Experimental procedures

To assess the evidence on the use of cannabidiol in the treatment of psychotic disorders, we performed a search for English articles using Medline and EMBASE. Search items included “cannabidiol and treatment”, “cannabidiol and psychosis” and “cannabidiol and schizophrenia”. Each citation was evaluated by reading title and abstract and determining relevance and eligibility. Studies were selected if they described experiments with psychosis models, psychotic symptoms or psychotic disorders as outcome measure and involved CBD as intervention. Additional studies were identified by searching reference lists of previously identified studies. Studies of other ligands of cannabinoid receptors were not selected. In total 66 studies on the CBD and psychosis (models) were selected. Additionally several studies on the role of the ECS in psychosis were also reviewed.

3. Endocannabinoid system

CBD is one of the phytocannabinoids that interacts with the ECS. The ECS consists of cannabinoid receptors, endogenous cannabinoids and several enzymes controlling activation and availability of these endocennabinoids (Pertwee, 2008). The ECS has a role in several physiological processes such as memory (Hampson and Deadwyler, 1999), appetite (Di Marzo et al., 2001) and stress responses (Hill et al., 2010).

Five endogenous cannabinoids have been identified (Devane et al., 1992) that bind to CB1 or CB2 receptors. However, so far only the two most relevant endocannabinoids seem to play a relevant role in ECS functioning namely 2-arachidonoylglycerol (2-AG) and anandamide (N-arachidonoylethanolamine or AEA).

2-AG is a full agonist of CB1r (Mechoulam et al., 1970; Castillo et al., 2012; Pertwee, 2008), AEA is a partial agonist of CB1r (Howlett, 2002; Howlett et al., 2004). These endocannabinoids are polyunsaturated fatty acid derivates. Endocannabinoids are thought to act as retrograde synaptic messengers. After neurotransmitters such as glutamate and γ-aminobutyric acid (GABA) induce a postsynaptic increase of intracellular calcium they are released postsynaptically and inhibit the presynaptic release of these neurotransmitters by binding to cannabiboid receptors (Pertwee, 2008). Availability and actions of endocannabinoids are controlled

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by enzymes involved with synthesis and degradation, such as fatty acid amide hydrolase (FAAH) and monoglycerol lipase (MGL) (Ueda et al., 2011).

The two cannabinoid receptors CB1 and CB2 have distinct features. The CB1 receptor is the most prominent G-coupled endocannabinoid receptor in the central nervous system (CNS) (Marco et al., 2011). It is a transmembrane receptor that converts extracellular stimuli into downstream intracellular signaling pathways such as downregulation of cAMP (following inhibition of adenylyl cyclase), activation of MAP kinase and inhibition of voltage-gated Ca^{2+} channels (Howlett, 2002; Howlett et al., 2004). CB1 receptors inhibit release of excitatory and inhibitory neurotransmitters such as acetylcholine, noradrenaline, GABA, glutamate and dopamine (Freund et al., 2003). Further downstream effects of these signaling pathways are complex and numerous and are beyond the scope of this paper, for review see Howlett et al. (2010). CB1 receptors are found in the central and peripheral nervous system, but also in other organs such as digestive system tissue and the respiratory tract. Expression of CB1r is particularly abundant in nerve terminals in the cerebellum, hippocampus, basal ganglia and frontal cortex but is also prevalent in the basolateral amygdala, hypothalamus and midbrain (Mailleux et al., 1992; Glass et al., 1997; Herkenham et al., 1991). The expression of CB1r is not limited to neurons (Marco et al., 2011) but is also observed on glia cells (Sanchez et al., 1998; Waksman et al., 1999; Walter et al., 2003). The CB1 receptor is thought to play a key role in mediating acute psychotic experiences associated with cannabis use (Huestis et al., 2001).

In contrast to CB1, the expression of CB2 receptors is most prominent in the immune system (Munro et al., 1993; Galiegue et al., 1995) where they act as immunomodulators (Onaivi et al., 2006). Recent data demonstrate however that CB2 receptors are also expressed in the CNS, most prominently on microglia, the immune cells of the brain (Van Sickle et al., 2005; Gong et al., 2006; Onaivi et al., 2006; Garcia-Gutierrez and Manzanares, 2011).

Recently, other receptors besides CB1r and CB2r were found to be involved in endocannabinoid signaling. Two of these orphan G protein-coupled receptors are GPR119 (mainly expressed in the digestive tract) and GPR55 (CNS and bone). Moreover vanilloid type 1 (TRPV1) ion channels are also activated by endogenous cannabinoids (in the CNS) (Henstridge et al., 2011; Brown, 2007; Starowicz et al., 2008; Balenga et al., 2011). The vanilloid receptor is a nonselective cation channel that has been studied extensively for involvement in nociception (Cui et al., 2006; Huang et al., 2002). It was already known that CBD is capable of binding to TRPV1 (Bisogno et al., 2001) and that endocannabinoids also activate TRPV1 (Brown, 2007). Several recent studies suggest intensive interplay between vanilloid and endocannabinoid systems in several behavioral functions including anxiety (Umathe et al., 2012; Fogaca et al., 2012).

Besides endocannabinoids a number of non-endogenous compounds also interact with the ECS. These exocannabinoids include the phytocannabinoids (such as CBD and THC) and synthetic cannabinoids (such as the CB1R antagonist Rimonabant).

Due to on demand nature of endocannabinoid signaling, exogenous cannabinoids target CB1 and CB2 receptors in a less selective manner than endocannabinoids. THC is a partial CB1r and CB2r agonist, but with less affinity than AEA. Interaction with inhibitory or excitatory neurotransmitters, THC exerts a mixed inhibitory-excitatory effect on neuronal activity in different brain areas (Pertwee, 2008).

3.1. Endocannabinoid system and psychotic disorders

Two main lines of evidence suggest that the ECS is involved in the neuropathology of psychotic disorders, firstly studies on endo- and exo-cannabinoids and secondly studies on cannabinoid receptors.

3.1.1. The role of cannabinoids in psychotic disorders

A series of studies exploring the role of endogenous cannabinoids in the neurobiology of schizophrenia revealed that levels of endocannabinoids are markedly increased in cerebrospinal fluid (CSF) (Giuffrida et al., 2004; Koethe et al., 2009; Leweke et al., 1999; Leweke et al., 2007) and peripheral blood (De Marchi et al., 2003; Leweke et al., 2012) of schizophrenia patients. Moreover, increased levels of the endocannabinoid AEA appear to be reversed at clinical remission by antipsychotic therapy (De Marchi et al., 2003; Leweke et al., 2012). The authors suggest that the rise in AEA could represent reactive inhibitory feedback to over-activation of dopamine D2 receptors (Leweke et al., 2012). Furthermore, Leweke and colleagues found that schizophrenia patients that regularly use cannabis have lower AEA levels than schizophrenia patients that do not use cannabis. These findings lead to the hypothesis that cannabis use causes downregulation of AEA signaling in schizophrenia patients which may in turn facilitate psychosis (Giuffrida et al., 2004; Leweke et al., 2012).

Besides the role of endocannabinoids in the neurobiology of psychotic disorders, a large number of studies address the role of exocannabinoids in the development of psychotic disorders. Exposure to THC can cause acute transient psychotic symptoms in healthy individuals and schizophrenia patients (D'Souza et al., 2005; Stone et al., 2012; Morrison et al., 2011). This effect might be related to dopamine release in the striatum following THC exposure as shown in several studies in humans (Bossong et al., 2008; Bhattacharyya et al., 2012a, 2012c) and in the nucleus accumbens and prefrontal cortex in several animal models (J. Chen et al., 1990; J.P. Chen et al., 1990; Tanda et al., 1997; Diana et al., 1998; Verrico et al., 2004). However, it is still debated if this is indeed a dopamine mediated pathway since negative studies have also been presented (Barkus et al., 2011; Kuepper et al., 2010; D'Souza et al., 2008; Stokes et al., 2009).

As described above, blockade of the CB1 receptor results in inhibition of the acute psychological effects associated with cannabis use, suggesting a key role for CB1r in mediating cannabis associated phenomena (Huestis et al., 2001).

Although the association between cannabis and psychosis is part of an ongoing debate (Macleod et al., 2004; Arseneault et al., 2002; Minozzi et al., 2010), a long term effect of cannabinoids is suggested by studies implying cannabis as a risk factor for psychotic disorders. Several epidemiological studies on Psychotic Like Experiences (PLEs) (Schubart et al., 2010; Arseneault et al., 2004; van Gastel et al., 2012) but also psychotic disorders

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(Moore et al., 2007), several imaging studies (Rais et al., 2008; Rapp et al., 2012; Yücel et al., 2008) and gene-environment studies (Caspi et al., 2005; Di Forti et al., 2012; Henquet et al., 2006; van Winkel, 2011) contribute to this notion. In addition, the course of disease is significantly worsened in schizophrenia patients that regularly use cannabis (Linszen et al., 1994; Faber et al., 2012; Grech et al., 2005).

3.1.2. The role of cannabinoid receptors in psychotic disorders

The second line of evidence that links the ECS with psychotic illness comes from studies on the role of the CB1 and CB2 receptors in schizophrenia. A series of post-mortem studies investigated changes in the expression of cannabinoid receptors associated with schizophrenia. Dean et al. (2001) found an increase in cannabinoid-1 receptors in the dorsolateral prefrontal cortex of schizophrenia patients compared with healthy controls (independent of cannabis use) and an increase in the density of cannabinoid-1 receptors in the caudate–putamen in response to cannabis use, independent of diagnosis. In contrast, in another postmortem study, Eggan et al. found that in the dorsolateral pre-frontal cortex levels of CB1R mRNA were significantly lower in subjects with schizophrenia. Since impaired cognitive functioning in schizophrenia is associated with reduced GABA neurotransmission, the authors hypothesize that reduced CB1r mRNA and protein levels in schizophrenia patients represent a compensatory mechanism to increase GABA transmission in order to normalize working memory function (Eggan et al., 2008). A different study revealed that antipsychotic treatment induces down-regulation of CB1 receptors in the prefrontal cortex. The authors of this study also suggest that this response to antipsychotic treatment could represent an adaptive mechanism that reduces the endocannabinoid-mediated suppression of GABA release to normalize cognitive dysfunctions (Urigüen et al., 2009).

Also using postmortem material, Zavitsanou et al. examined the distribution and density of CB1 receptors in the left anterior cingulate cortex (ACC) in patients with schizophrenia and matched controls. A significant increase in CB1 receptors was found in the schizophrenia group as compared to the control group, suggesting that changes in the endogenous cannabinoid system in the ACC may be involved in the pathology of schizophrenia (Zavitsanou et al., 2004). Moreover, Newell et al. (2006) demonstrated an increase in CB1 receptor density in the superficial layers of the posterior cingulate cortex in schizophrenia (independent of cannabis use). Moreover, in a autoradiography study using postmortem samples, Jenko et al. (2012) compared CB1r binding in the dorsolateral prefrontal cortex (DLPFC) from schizophrenia patients to healthy controls and found that CB1 binding was 20% higher in patients than in controls. This finding was replicated by a different group, replicating a main effect of diagnosis across all layers of the DLPFC whereby patients showed 22% higher levels of CB1r binding (Dalton et al., 2011). Finally, in an in vivo study using a novel PET tracer ([(11)C]OMAR (JHU75528)), Wong et al. (2010) observed elevated mean CB1 binding receptors in patients with schizophrenia in all regions.

In conclusion, although at times paradoxical, available data suggest that schizophrenia is associated with the expression of cannabinoid receptors in different brain areas.

A different approach that implicates a role for the CB receptors in the development of psychosis comes from a series of studies investigating the impact of polymorphisms of the CNR1 gene, coding for the CB1 receptor, on the risk to develop psychotic illness.

Ujike et al. found that the presence of AAT-repeat microsatellite in the CNR1 gene is significantly associated with schizophrenia, particularly the hebephrenic subtype. This finding was corroborated in other independent samples (Ujike et al., 2002; Chavarria-Siles et al., 2008; Martinez-Gras et al., 2006). However, negative findings have also been reported on this AAT triplet (Tsai et al., 2000). Recently, a SNP in CNR1 (rs12720071) was found to moderate the impact of cannabis use on white matter volumes and cognitive impairment in schizophrenia patients, also suggesting gene–environment interaction (Ho et al., 2011).

The CB2 receptor is predominantly expressed on hematopoietic cells. This indicates that the endocannabinoid system may play an important role in the immune system, see also a reviews by Basu and Dittel (2011) and Cabral and Griffin-Thomas (2009). Moreover, cannabis is known for its medicinal use in inflammatory and asthma conditions since prehistoric times, but cannabis usage may also lead to decreased resistance to various infectious agents. It is therefore thought that the endocannabinoid system has an important role in regulating several processes in the immune system. Furthermore, growing evidence indicates that the immune system is involved in the pathogenesis of psychotic disorders, including schizophrenia and bipolar disorder (Muller et al., 2000; Beumer et al., 2012). Examples are association with variations genes involved in the immune system (Stefansson et al., 2009) and altered cytokine profiles in serum (Doorduin et al., 2009) and activation of microglia in patients with schizophrenia (van Berckel et al., 2008). Using CB-1 and/or -2 knockout mice, selective CB-2 agonists/antagonists and in vitro systems these regulatory processes have been investigated (Basu and Dittel, 2011; Cabral and Griffin-Thomas, 2009). It was shown that CB2r is involved in development of different types of immune cells and administration of cannabidiol to rats leads to decreased numbers of T- and B-cell subsets (Ignatowska-Jankowska et al., 2009). The described role of CB2r in immune responses encourage us to hypothesize that the endocannabinoid system may be involved in the pathogenesis of psychotic disorders via altering regulatory mechanisms in the immune system. It is clear however, that regulation of immune responses via CB-2 is complex and needs further studies.

Besides in immunological functioning, the CB2 receptor is also involved in other biological processes that are associated with schizophrenia. A recent genetic association study in two independent populations suggested an increased risk of schizophrenia in people with a single nucleotide polymorphism (SNP) leading to low CB2 receptor function (Ishiguro et al., 2010). Furthermore, De Marchi et al. (2003) reported that CB2R mRNA levels were diminished in peripheral blood mononuclear cells in patients with schizophrenia after treatment with olanzapine. The authors argue that, since CB2R expression is subject to

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downregulation in activated macrophages and leukocytes (Klein et al., 2001), the decrease of CB2R mRNA levels could be a consequence of reduced activity of blood leukocytes.

4. Cannabidiol and the endocannabinoid system

Although CBD has very low affinity for CB1 and CB2 receptors, Pertwee and colleagues found that CBD is capable of altering CB1R/CB2R function at relatively low concentrations by antagonizing CB1/CB2 receptor agonists such as AEA and 2-AG (Thomas et al., 2007; Pertwee, 2008). CBD could therefore also be able to interfere with the impact of THC on the ECS, providing a biological basis for the notion that the THC/CBD ratio in cannabis products might moderate the risk of cannabis associated adverse, effects described elsewhere in this paper. Moreover, CBD reduces the cellular uptake of AEA (Bisogno et al., 2001; Leweke et al., 2012). Given the previously mentioned hypothesis on the role of AEA in counteracting dopamine D2 receptor overactivity, CBD may have antipsychotic capacities by increasing synaptic AEA to indeed counteract D2 overactivation.

5. Cannabidiol and the immune response

Finally, as described above, cannabidiol may also have an attenuating role in immune responses associated with psychotic disorders (De Filippis et al., 2011). Various studies demonstrated that the endocannabinoid system is involved in chemotaxis and migration of immune cells, including microglia cells. CBD was shown to decrease the number of mast cells and macrophages in inflammatory bowel models (De Filippis et al., 2011). Exogenous cannabinoids, including cannabidiol (Kaplan et al., 2008), inhibit the production of pro-inflammatory cytokines and shift the cytokine profile from a T-helper 1 response to a T-helper 2 response. This is interesting, since schizophrenia has been associated with a T-helper 2 skewed immune profile (Muller et al., 2000). Most interestingly, different experimental and animal studies demonstrated that cannabidiol inhibits microglia activation (Kozela et al., 2010, 2011; Martin-Moreno et al., 2011). Moreover, cannabinoids have neuroprotective effects in several rodent models of neurologic diseases that have an inflammatory component, such as multiple sclerosis (Cabral and Griffin-Thomas, 2009). Furthermore, cannabidiol administration in an experimental meningitis model decreased the production of pro-inflammatory cytokines and prevented memory impairment (Barichello et al., 2012). Other immune regulatory mechanisms that have been described for cannabinoids are suppression of humoral responses, macrophage activity, T-cell responses and NK cytolytic killing (Basu and Dittel, 2011; Cabral and Griffin-Thomas, 2009).

6. Cannabidiol as an antipsychotic agent

The remainder of this paper will focus on different lines of evidence on the antipsychotic potential of CBD. Table 1 provides an overview of experimental human and animal studies of psychosis models.

6.1. Evidence from animal studies

The first animal studies investigating the effect of cannabidiol in translational psychosis phenotypes focused on the differential impact of THC and CBD on a number of these behavioral phenotypes. Mechoulam et al. (1970) reported that CBD did not induce a range of behavioral changes that was associated with THC exposure in rhesus monkeys, a finding that was later corroborated in a rat model (Fernandes et al., 1974).

Since the dopamine transmission system is thought to play a key role in psychosis (Howes and Kapur, 2009; Fusar-Poli and Meyer-Lindenberg, 2012a, 2012b), several dopamine based animal models of psychosis were proposed as a mean to study the pathophysiology of psychosis in animals. Examples of such models are apomorphine, cocaine or amphetamine induced stereotypic behavior and hyperlocomotion. Additionally, glutamate N-methyl-D-aspartate (NMDA) antagonists such as ketamine, PCP or MK-801, are used for glutamate based psychosis models (Lipska and Weinberger, 2000). THC and CBD have demonstrated to have very different effects in several murine psychosis models. Evidence was found that CBD does not only exert very different effects than THC, but is capable of reversing psychosis phenotypes. CBD reversed THC induced reduction of social interaction (Malone et al., 2009) and apomorphine induced sniffing, biting and stereotyped behavior in rats (Zuardi et al., 1991). CBD also attenuated dexamphetamine-induced hyperlocomotion in mice (Long et al., 2010). Furthermore, CBD was comparable to clozapine, and superior to haloperidol in attenuating ketamine induced hyperlocomotion in mice (Moreira and Guimaraes, 2005). This correcting effect of CBD on glutamate hypofunction was later corroborated in a similar study in rats, investigating MK-801 induced hyperactivity, deficits in prepulse inhibition and social withdrawal (Gururajan et al., 2011). In a sensory gating mouse model CBD has a similar efficacy as clozapine in reversing MK-801 induced prolonged PPI (Long et al., 2006). In an experimental design using pretreatment with the TRPV1 blokker capsazepine, this study demonstrated that this effect of CBD is probably mediated through the vanilloid type 1 receptor (TRPV1). It was already known that CBD is capable of binding to TRPV1 (Bisogno et al., 2001) and that endocannabinoids also activate TRPV1 (Brown, 2007). Several recent studies suggest intensive interplay between vanilloid and endocannabinoid systems in several behavioral functions (Umathe et al., 2012; Fogaca et al., 2012).

A different approach to evaluate the psychopharmacological profile of CBD is to compare the effect of CBD on c-fos mediated immunoreactivity to that of clozapine and haloperidol. Alteration in expression of the c-fos gene is viewed as an immediate-early marker for recent neuronal activity (Day et al., 2008). c-fos expression is increased in several brain regions in reaction to typical and atypical antipsychotics (Dragunow et al., 1995). Moreover, typical and atypical antipsychotics produce different activation patterns (Robertson and Fibiger, 1992). Using a rat model, Guimaraes et al. compared c-fos expression in the nucleus accumbens and the dorsal striatum in reaction to haloperidol, clozapine and CBD. Haloperidol

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Table 1 Summary of studies investigating the effect of CBD in experimental animal and human psychosis models.

Subjects	Method	CBD dose	Results	Reference
Animal psychosis models				
Rats	Apomorphine induced hyperlocomotion	60 mg/kg	Reduction	Zuardi et al. (1991)
Rats	C-Fos expression	120 mg/kg	Increase in nucleus accumbens	Guimaraes et al. (2004)
Mice	D-amphetamine induced stereotypy	30–60 mg/kg	Reduction	Moreira and Guimaraes (2005)
Mice	MK-801 induced disruption of PPI	5 mg/kg	Reduction	Long et al. (2006)
Human studies				
Nine healthy subjects	Nabilone induced disruption of binocular depth inversion	200 mg	Reduction	Leweke et al. (2000)
Ten healthy subjects	Ketamine induced dissociative- and psychotic-symptoms	600 mg	Reduction of dissociative symptoms	Hallak et al. (2011)
Twenty-two healthy subjects	Auditory evoked mismatch negativity	5.4 mg	Increase	Juckel et al. (2007)
Treatment studies				
One schizophrenia patient	Case study	1200 mg/day	Symptom improvement	Zuardi et al. (1995)
Three treatment resistant schizophrenia patients	Case study	40–1280 mg/day	Mild symptom improvement in one patient	Zuardi et al. (2006)
Six patients with Parkinson's disease and psychotic symptoms	Case study	150 mg/day	Significant improvement	Zuardi et al. (2009)
Two patients with bipolar disease	Case study	600–1200 mg/day	No improvement of symptoms	Zuardi et al. (2010)
Forty-two acute paranoid schizophrenia patients	Double-blind, randomized clinical trial of cannabidiol vs. amisulpride	800 mg of CBD or amisulpride	Equally significant clinical improvement, cannabidiol displayed a markedly superior side effects	Leweke et al. (2012)

induced c-fos expression in the nucleus accumbens (limbic region) and in the dorsal striatum. In contrast CBD and clozapine only induced activation in the nucleus accumbens. Moreover, CBD did not induce catalepsy, as haloperidol did, and showed very low potency to increase prolactin levels. The similarity in activation patterns between CBD and clozapine is an argument for the possible relatedness in mechanism of action between atypical antipsychotics and CBD (Zuardi et al., 1991; Guimaraes et al., 2004).

6.2. Evidence from human experimental studies

One of the first studies comparing the psychomimetic effects of THC and CBD in humans was performed by Perez-Reyes et al. (1973). The investigators showed that compared to THC and cannabinol, CBD did not produce any psychological or physiological effects described as feeling "high". Karniol et al. (1974) showed in 1974 that simultaneous exposure to CBD blocks THC induced effects on pulse rate, time production tasks and psychological reactions as anxiety or panic. Zuardi et al. (1982) were the first to demonstrate that post-treatment with CBD is capable of reducing THC induced effects, particularly anxiety (Crippa al., 2009). In a more recent study, Hallak et al. (2011) found a non-significant trend of CBD to reduce ketamine-induced depersonalization in healthy subjects. In a study investigating the effect of CBD on THC induced behavioral measures such as euphoria and psychomotor impairment, Dalton et al. (1976) found that although pretreatment with CBD did not alter THC induced effects, simultaneous exposure to CBD did. In a small study by Bhattacharyya et al. (2009)), healthy volunteers underwent CBD pretreatment before THC admission, which successfully blocked the emergence of psychotic symptoms measured by the Positive and Negative Syndrome scale (PANSS) (Kay et al., 1987). Sensorimotor gating of startle response provides a further valuable and validated model of psychosis (Braff et al., 2001). In contrast to the animal studies described above, one study reported that CBD did not alter THC induced subjective reports, measures of cognitive task performance, electroencephalography (EEG) and event-related potential (ERP)

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in humans (Ilan et al., 2005). In parallel, CBD failed to demonstrate a reversal of Δ9-THC-induced P300 reduction in humans (Roser et al., 2008). However, one possible explanation for these contrasting findings is provided by Stadelmann et al. (2011) who argue that variation in CNR1 genotypes might differentially alter the sensitivity to the acute effects of cannabinoids on P300 generation in healthy subjects.

A therapeutic effect of CBD is also suggested by a study comparing the effects of THC and CBD in an evoked mismatch negativity (MMN) model. MMN is an auditory ERP that represents a measure of automatic context-dependent information processing and auditory sensory memory. A meta-analysis showed that MMN deficits are a robust feature in chronic schizophrenia and indicate abnormalities in automatic context-dependent auditory information processing and auditory sensory memory (Umbricht and Krljes, 2005). Significantly greater MMN amplitude values at central electrodes were found under cannabis extract, but not with pure THC in 22 healthy subjects. These greater MMN amplitudes may imply higher cortical activation and cognitive performance related to the positive effects of CBD (at doses of 5.4 mg/kg) (Juckel et al., 2007). A final, well studied experimental model for psychosis is binocular depth inversion (Schneider et al., 2002). Leweke et al. investigated the capability of CBD to attenuate effects of the synthetic THC like CB1 receptor agonist nabilone on binocular depth inversion in nine healthy subjects. They found that CBD (200 mg) clearly reversed nabilone induced effects (Leweke et al., 2000). All the studies mentioned above were performed in healthy volunteers.

7. Evidence from imaging studies

Studies investigating cannabis related changes in brain tissue composition provide markedly divergent results (Yücel et al., 2008; Matochik et al., 2005). Demirakca provided evidence for the idea that the THC/CBD ratio plays an explanatory role for these contrasting results. They found an inverse correlation between the THC/CBD ratio in hair samples of cannabis users and hippocampal volume suggesting a protective effect of cannabidiol. Differences in THC/CBD ratio between studies can potentially also explain previous divergence in cannabis associated patterns of brain tissue composition (Demirakca et al., 2011).

A series of studies by Bhattacharyya and colleagues in 15 healthy volunteers describe effects of THC and CBD on cerebral activation (measured with fMRI) in relation to phenomenological measures of anxiety and psychotic symptoms. A response inhibition task showed that THC attenuates the engagement of brain regions that mediate response inhibition and that CBD modulated function in the left lateral temporal cortex and insula, regions not usually implicated in response inhibition (Borgwardt et al., 2008). A different analysis showed that verbal paired associate learning was not modulated by THC nor CBD, however in this study THC modulated mediotemporal and ventrostriatal function and simultaneously induced psychotic symptoms suggesting that this might be an underlying neurobiological pathway in the association between THC and psychotic symptoms (Bhattacharyya et al., 2009). When exposing the subjects to fearful faces, THC and CBD had significantly distinct effects on response to emotional processing (Fusar-Poli et al., 2009). Interestingly, CBD but not THC disrupted forward connectivity between the amygdala and the anterior cingulate, providing a first neurophysiological model for the anxiolytic properties attributed to CBD (Fusar-Poli et al., 2010). Investigating local brain activation patterns under THC and CBD during several experimental conditions, the investigators found that THC and CBD had opposite effects on the activation of several brain regions. These opposing effects were described in the occipital cortex during visual tasks, in the superior temporal cortex while listening to speech, in the amygdale viewing fearful faces, in the striatum during verbal recall and in the hippocampus during the response inhibition task (Bhattacharyya et al., 2010). Moreover, THC and CBD had opposite effects on activation of the right posterior superior temporal gyrus, which is the right-sided homolog of Wernicke's area but also in areas that are involved in the processing of auditory and visual stimuli and related to induced psychotic symptoms measured with the PANSS (Winton-Brown et al., 2011). Finally this group investigated the effects of THC and CBD on attentional salience processing and found that THC induced psychotic symptoms (measured with the PANSS) that were related to striatal activation. They found that CBD had opposite effects to THC on activation of the striatum, prefrontal cortex and medial temporal cortex (Bhattacharyya et al., 2012b).

8. Evidence from epidemiological studies

Numerous studies show that psychotic outcomes are associated with cannabis use in a dose-dependent fashion (Moore et al., 2007; Stefanis et al., 2004; van Gastel et al., 2012; Skinner et al., 2010). The strength of this association might be influenced by cannabis potency, which can be defined in terms of the concentrations of THC and, inversely, CBD (Potter et al., 2008; Pijlman et al., 2005). Rottanburg et al. (1982) described a cohort with a relatively high (30%) percentage of psychotic symptoms that could be attributed to the use of cannabis variants with relatively low concentrations of cannabidiol. In an effort to assess the influence of different CBD concentrations in different cannabis products on the association between cannabis use and psychosis, Di Forti et al. (2009) compared cannabis use habits of 280 first episode psychosis patients with healthy cannabis users and found that patients with psychosis used higher-potency cannabis (with high concentrations THC and low concentrations CBD), for longer duration and with greater frequency. In a more direct approach, Morgan and Curran (2008) showed that cannabis users ($n=120$) who have a higher CBD content in hair samples, have fewer psychometric psychotic experiences, a result that was later replicated with a similar design in a different sample (Morgan et al., 2011). In a study investigating cannabis use associated cognitive performance, Morgan et al. (2010), found a clear, significant effect of CBD in attenuating THC induced deficits in memory performance. In a larger sample ($n=1877$), Schubart et al. (2011) demonstrated that habitual use of cannabis with relatively high concentrations of CBD is associated with the experience of

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fewer psychotic experiences than the use of low CBD cannabis types.

9. Clinical studies

Zuardi and colleagues published several reports on the therapeutic use of CBD monotherapy in patients with psychotic symptoms. In a case report, successful treatment with 1200 mg/day CBD was described in a 19 year old woman with schizophrenia (Zuardi et al., 1995). In a short report, therapy of three treatment resistant schizophrenia patients with escalating doses up to 1280 mg/day of CBD was described, of whom only one patient showed mild symptom improvement (Zuardi et al., 2006). The authors speculate that a low initial CBD dose and the treatment resistance in these patients, might explain this negative finding. A pilot study investigating the effects of CBD in six patients with Parkinson's disease and psychotic symptoms, demonstrated a significant improvement of psychotic symptoms, without worsening motor functioning or cognition (Zuardi et al., 2009). In another pilot study in patients with acute manic episodes, there was no evidence of a benefit of CBD, suggesting that the efficacy is confined to non-affective psychosis (Zuardi et al., 2010).

Finally, Leweke et al. reported the first double-blind controlled clinical trial in 42 acute paranoid schizophrenia or schizophreniform disorder patients comparing CBD with amisulpride in treatment during 4-weeks. They found that the therapeutic effect of CBD in reducing psychotic symptoms, measured with the Positive and Negative Syndrome scale (PANSS) was similar to amisulpride. However, CBD treatment was accompanied with significantly less extrapyramidal side effects, prolactine increase and weight gain than amisulpride (Leweke et al., 2012). Moreover, the authors report an association between higher AEA levels and clinical improvement within subjects treated with CBD. Since CBD has the capability to inhibit FAAH and, as mentioned above, FAAH activity reduces AEA concentrations, the authors suggest that inhibition of FAAH activity by CBD might be a functionally relevant component of its antipsychotic properties (Leweke et al., 2012).

10. Tolerability

Extensive in vivo and in vitro reports of CBD administration across a wide range of concentrations did not detect important side or toxic effects, and in addition, the acute administration of this cannabinoid by different routes did not induce any significant toxic effect in humans (Bergamaschi et al., 2011). With a median Lethal Dose (LD_{50}) of 212 mg/kg in rhesus monkeys, CBD has a low toxicity (Rosenkrantz et al., 1981). Bergamaschi et al. (2011) demonstrated that CBD is well tolerable up to doses of 1500 mg/day. Some studies investigated mutagenic or teratogenic effects and describe no such events (Matsuyama and Fu, 1981; Dalterio et al., 1984).

11. Conclusion

In summary, evidence from several study domains suggests that CBD has some potential as an antipsychotic treatment.

Animal studies show that CBD is capable of reversing various THC induced psychosis like behaviors in dopaminergic but also glutamatergic animal models of psychosis (Fernandes et al., 1974; Malone et al., 2009; Zuardi et al., 1991; Long et al., 2010; Moreira and Guimaraes, 2005; Gururajan et al., 2011). In addition, these studies found that the vanilloid (TRPV1) receptor is likely to play an important role in CBD action (Long et al., 2006) and some provided evidence for the notion that CBD has a neuropharmacological profile that is similar to atypical antipsychotics (Guimaraes et al., 2004).

Human studies found that THC and CBD have very distinct effects on several psychological and physiological parameters associated with psychosis (Perez-Reyes et al., 1973;Karniol et al., 1974). Moreover CBD is capable of reversing THC induced psychological effects (Zuardi et al., 1982;Hallak et al., 2011; Dalton et al., 1976) and preliminary data suggest that (pre-treatment) with CBD is capable of reducing THC induced psychological effects (Bhattacharyya et al., 2012a, 2012b, 2012c). Imaging studies also provide various clues on a potential antipsychotic effect of CBD.

A volumetric MRI study found CBD to have a protective effect on cannabis use associated hippocampus volume loss (Demirakca et al., 2011). Functional imaging studies showed that during tasks relevant to psychosis, THC and CBD have opposite effects on regional brain activation in various areas such as the striatum, the prefrontal cortex and the medial temporal cortex, areas that are associated with the pathophysiology of psychotic disorders (Bhattacharyya et al., 2009, 2010, 2012a, 2012b, 2012c; Borgwardt et al., 2008; Winton-Brown et al., 2011).

Several epidemiological studies investigated differences in effects of cannabis type that contain different concentrations of CBD. Cannabis types containing more CBD consistently cause less psychotic like experiences in the general population (Schubart et al., 2011; Di Forti et al., 2009; Morgan et al., 2010; Morgan and Curran, 2008).

A series of relatively small clinical studies in different patient subcategories, published by Zuardi and colleagues overall, suggest that CBD might have antipsychotic properties (Zuardi et al., 1995, 2006). Currently, the first and only clinical trial ($n=42$) compared CBD to amisulpride and clearly showed that CBD is capable of reducing psychotic symptoms equally effective to amisulpride but with significantly less side effects.

Biological models that explain the potential antipsychotic effects of cannabidiol vary from interference with ECS functioning by inhibition of FAAH activity (Leweke et al., 2012) to immunological properties of CBD that might moderate immunological processes involved in the pathophysiology of psychotic disorders.

Given the high tolerability and superior cost-effectiveness, CBD may prove to be an attractive alternative to current antipsychotic treatment, possibly in specific subgroups of patients. However, to date the vast majority of the current evidence comes from experimental non-clinical studies and case reports. Although promising, this does not provide evidence that CBD has antipsychotic properties. Therefore, the only clinical evidence currently available for CBD as an antipsychotic agent is the relatively small ($n=42$) clinical trial published by Leweke et al. (2012). A large double blind randomized clinical trial in a new study

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population, comparing CBD to an atypical antipsychotic agent is required to truly advance the field. Moreover, illuminating pharmacological pathways through which CBD reduces the experience of psychotic symptoms could also lead to the design of new synthetic agents that act through the endocannabinoid system in ameliorating psychotic symptoms.

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Contributors

C. Schubart was involved in the literature search, drafting and revising the paper. I. Sommer was involved in designing the conceptual framework and revision of the paper. P. Fusar-Poli performed a literature search, was involved in designing the conceptual framework and revision of the paper. L. de Witte contributed to drafting, the conceptual framework and revision of the paper. R. Kahn revised the paper. M. Boks was involved in designing the conceptual framework, writing and revision of the paper.

Conflicts of interest

None of the authors of the above manuscript have any conflict of interest which may arise from being named as an author on the manuscript or receive any financial support that could potentially affect the reporting of the study.

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